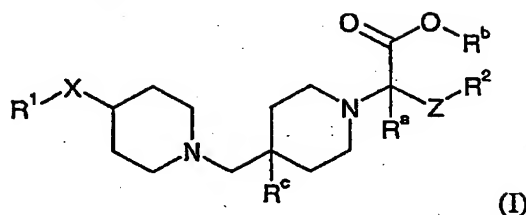


CLAIMS

1. A compound of formula (I):



wherein:

$R^a$  and  $R^b$  are, independently, hydrogen or  $C_{1-4}$  alkyl or  $R^a$  forms part of a ring as defined below;

$R^c$  is hydrogen or hydroxy;

$X$  is  $CH_2$ ,  $C(O)$ ,  $O$ ,  $S$ ,  $S(O)$ ,  $S(O)_2$  or  $NR^3$ ;

$Z$  is  $CHR^d(CH_2)_n$ ;

$n$  is 0 or 1;

$R^d$  is hydrogen,  $C_{1-4}$  alkyl, hydroxy or  $C_{1-4}$  alkoxy;

$R^1$  is hydrogen,  $C_{1-6}$  alkyl, aryl or heterocyclyl;

$R^2$  is aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, cyano, nitro, hydroxy, oxo,  $S(O)_p R^4$ ,

$OC(O)NR^5 R^6$ ,  $NR^7 R^8$ ,  $NR^9 C(O)R^{10}$ ,  $NR^{11} C(O)NR^{12} R^{13}$ ,  $S(O)_2 NR^{14} R^{15}$ ,

$NR^{16} S(O)_2 R^{17}$ ,  $C(O)NR^{18} R^{19}$ ,  $C(O)R^{20}$ ,  $CO_2 R^{21}$ ,  $NR^{22} CO_2 R^{23}$ ,  $C_{1-6}$  alkyl,  $CF_3$ ,  $C_{1-6}$

alkoxy( $C_{1-6}$ )alkyl,  $C_{1-6}$  alkoxy,  $OCF_3$ ,  $C_{1-6}$  alkoxy( $C_{1-6}$ )alkoxy,  $C_{1-6}$  alkylthio,  $C_{2-6}$

alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-10}$  cycloalkyl (itself optionally substituted by  $C_{1-4}$  alkyl or

oxo), methylenedioxy, difluoromethylenedioxy, phenyl, phenyl( $C_{1-4}$ )alkyl,

phenoxy, phenylthio, phenyl( $C_{1-4}$ )alkoxy, heterocyclyl, heterocyclyl( $C_{1-4}$ )alkyl,

heterocycliloxy or heterocyclyl( $C_{1-4}$ )alkoxy; wherein any of the immediately

foregoing phenyl and heterocyclyl moieties are optionally substituted with halogen,

hydroxy, nitro,  $S(O)_q(C_{1-4}$  alkyl),  $S(O)_2 NH_2$ ,  $S(O)_2 NH(C_{1-4}$  alkyl),  $S(O)_2 N(C_{1-4}$

alkyl) $_2$  (and these alkyl groups may join to form a ring as described for  $R^5$  and  $R^6$

below), cyano,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy,  $C(O)NH_2$ ,  $C(O)NH(C_{1-4}$  alkyl),  $C(O)N(C_{1-4}$

alkyl) $_2$  (and these alkyl groups may join to form a ring as described for  $R^5$  and  $R^6$

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below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHC(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$ ;

or Z,  $\text{R}^2$  and  $\text{R}^a$  together with the carbon atom to which Z and  $\text{R}^a$  are attached form a ring;

5 p and q are, independently, 0, 1 or 2;

$\text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{R}^{12}, \text{R}^{13}, \text{R}^{14}, \text{R}^{15}, \text{R}^{16}, \text{R}^{18}, \text{R}^{19}, \text{R}^{20}, \text{R}^{21}$  and  $\text{R}^{22}$  are, independently, hydrogen,  $\text{C}_{1-6}$  alkyl (optionally substituted by halogen, hydroxy or  $\text{C}_{3-10}$  cycloalkyl),  $\text{CH}_2(\text{C}_{2-6} \text{ alkenyl})$ , phenyl (itself optionally substituted by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{S(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{NH}_2$ ,  $\text{S(O)}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C(O)NH}_2$ ,  $\text{C(O)NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHC(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$ ) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{S(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{NH}_2$ ,  $\text{S(O)}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C(O)NH}_2$ ,  $\text{C(O)NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHC(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C(O)}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$ );

alternatively  $\text{NR}^5\text{R}^6$ ,  $\text{NR}^7\text{R}^8$ ,  $\text{NR}^{12}\text{R}^{13}$ ,  $\text{NR}^{14}\text{R}^{15}$ ,  $\text{NR}^{18}\text{R}^{19}$ , may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by  $\text{C}_{1-4}$  alkyl on the distal nitrogen;

$\text{R}^4$ ,  $\text{R}^{17}$  and  $\text{R}^{23}$  are, independently,  $\text{C}_{1-6}$  alkyl (optionally substituted by halogen, hydroxy or  $\text{C}_{3-10}$  cycloalkyl),  $\text{CH}_2(\text{C}_{2-6} \text{ alkenyl})$ , phenyl (itself optionally substituted by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  above),  $\text{S(O)}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{NH}_2$ ,  $\text{S(O)}_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S(O)}_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^5$  and  $\text{R}^6$  above), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,

C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl), C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may  
 join to form a ring as described for R<sup>5</sup> and R<sup>6</sup> above), CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> alkyl),  
 NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>) or  
 heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH<sub>2</sub>, NH(C<sub>1-4</sub>  
 5 alkyl), N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described  
 for R<sup>5</sup> and R<sup>6</sup> above), S(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH(C<sub>1-4</sub> alkyl),  
 S(O)<sub>2</sub>N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for  
 R<sup>5</sup> and R<sup>6</sup> above), cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl),  
 C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for  
 10 R<sup>5</sup> and R<sup>6</sup> above), CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> alkyl), NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub>  
 alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>);  
 R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl or benzyl;  
 or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate  
 thereof.

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2. A compound of formula (I) as claimed in claim 1 wherein X is O.

3. A compound of formula (I) as claimed in claim 1 or 2 wherein the aryl and  
 heterocyclyl moieties of R<sup>1</sup> and R<sup>2</sup> are, independently, optionally substituted by:  
 20 halogen, cyano, nitro, hydroxy, oxo, S(O)<sub>p</sub>R<sup>4</sup>, OC(O)NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, NR<sup>9</sup>C(O)R<sup>10</sup>,  
 NR<sup>11</sup>C(O)NR<sup>12</sup>R<sup>13</sup>, S(O)<sub>2</sub>NR<sup>14</sup>R<sup>15</sup>, NR<sup>16</sup>S(O)<sub>2</sub>R<sup>17</sup>, C(O)NR<sup>18</sup>R<sup>19</sup>, C(O)R<sup>20</sup>, CO<sub>2</sub>R<sup>21</sup>,  
 NR<sup>22</sup>CO<sub>2</sub>R<sup>23</sup>, C<sub>1-6</sub> alkyl, CF<sub>3</sub>, C<sub>1-6</sub> alkoxy(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy or OCF<sub>3</sub>; p is 0, 1  
 or 2; R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup>  
 are, independently, hydrogen, C<sub>1-6</sub> alkyl (optionally substituted by halogen) or  
 25 phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH<sub>2</sub>, NH(C<sub>1-4</sub>  
 alkyl), N(C<sub>1-4</sub> alkyl)<sub>2</sub>, S(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH(C<sub>1-4</sub> alkyl),  
 S(O)<sub>2</sub>N(C<sub>1-4</sub> alkyl)<sub>2</sub>, cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl),  
 C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub>, CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> alkyl), NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub>  
 alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>); and R<sup>4</sup>, R<sup>17</sup> and R<sup>23</sup> are, independently, C<sub>1-6</sub>  
 30 alkyl (optionally substituted by halogen) or phenyl (itself optionally substituted by  
 halogen, hydroxy, nitro, NH<sub>2</sub>, NH(C<sub>1-4</sub> alkyl), N(C<sub>1-4</sub> alkyl)<sub>2</sub>, S(O)<sub>2</sub>(C<sub>1-4</sub> alkyl),  
 S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>N(C<sub>1-4</sub> alkyl)<sub>2</sub>, cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy,

C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl), C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub>, CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> alkyl),  
NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>).

4. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein R<sup>1</sup> is phenyl  
optionally substituted with halogen, cyano, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy.
5. A compound of formula (I) as claimed in claim 1, 2, 3 or 4 wherein R<sup>a</sup> is hydrogen.
6. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 wherein R<sup>b</sup> is  
hydrogen or methyl.
7. A compound of formula (I) as claimed in claim 1, 2, 3, 4, 5 or 6 wherein R<sup>c</sup> is  
hydrogen.
8. A compound of formula (I) as claimed in any preceding claim wherein R<sup>d</sup> is  
hydrogen, hydroxy or C<sub>1-4</sub> alkyl.
9. A compound of formula (I) as claimed in any preceding claim wherein Z is CH<sub>2</sub>,  
CH<sub>2</sub>CH<sub>2</sub>, CHCH<sub>3</sub> or CHOH.
10. A compound of formula (I) as claimed in any preceding claim wherein R<sup>2</sup> is phenyl  
or heterocyclyl optionally substituted by halogen, cyano, nitro, hydroxy, NR<sup>7</sup>R<sup>8</sup>, C<sub>1-6</sub>  
alkyl (optionally substituted with halogen), C<sub>1-6</sub> alkoxy (optionally substituted  
with halogen), S(O)<sub>p</sub>(C<sub>1-6</sub> alkyl), S(O)<sub>r</sub>CF<sub>3</sub> or S(O)<sub>2</sub>NR<sup>14</sup>R<sup>15</sup>; p and r are,  
independently, 0, 1 or 2; and R<sup>7</sup>, R<sup>8</sup>, R<sup>14</sup> and R<sup>15</sup> are, independently, hydrogen, C<sub>1-6</sub>  
alkyl (optionally substituted by halogen, hydroxy or C<sub>3-10</sub> cycloalkyl), CH<sub>2</sub>(C<sub>2-5</sub>  
alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH<sub>2</sub>,  
NH(C<sub>1-4</sub> alkyl), N(C<sub>1-4</sub> alkyl)<sub>2</sub>, S(O)<sub>2</sub>(C<sub>1-4</sub> alkyl), S(O)<sub>2</sub>NH<sub>2</sub>, S(O)<sub>2</sub>NH(C<sub>1-4</sub> alkyl),  
S(O)<sub>2</sub>N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for  
R<sup>7</sup> and R<sup>8</sup> below), cyano, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C(O)NH<sub>2</sub>, C(O)NH(C<sub>1-4</sub> alkyl),  
C(O)N(C<sub>1-4</sub> alkyl)<sub>2</sub> (and these alkyl groups may join to form a ring as described for  
R<sup>7</sup> and R<sup>8</sup> below), CO<sub>2</sub>H, CO<sub>2</sub>(C<sub>1-4</sub> alkyl), NHC(O)(C<sub>1-4</sub> alkyl), NHS(O)<sub>2</sub>(C<sub>1-4</sub>  
alkyl), C(O)(C<sub>1-4</sub> alkyl), CF<sub>3</sub> or OCF<sub>3</sub>) or heterocyclyl (itself optionally substituted

by halogen, hydroxy, nitro,  $\text{NH}_2$ ,  $\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ ,  $\text{S}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S}(\text{O})_2\text{NH}_2$ ,  $\text{S}(\text{O})_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{S}(\text{O})_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^7$  and  $\text{R}^8$  below), cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy,  $\text{C}(\text{O})\text{NH}_2$ ,  $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$  (and these alkyl groups may join to form a ring as described for  $\text{R}^7$  and  $\text{R}^8$  below),  $\text{CO}_2\text{H}$ ,  $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHC}(\text{O})(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{NHS}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$ ,  $\text{CF}_3$  or  $\text{OCF}_3$ ; or alternatively  $\text{NR}^7\text{R}^8$  or  $\text{NR}^{14}\text{R}^{15}$  may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by  $\text{C}_{1-4}$  alkyl on the distal nitrogen.

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11. A compound of formula (I) as claimed in any preceding claim wherein  $\text{R}^2$  is phenyl or heterocyclyl optionally substituted by halogen, cyano, hydroxy,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  haloalkyl or  $\text{C}_{1-4}$  alkoxy.

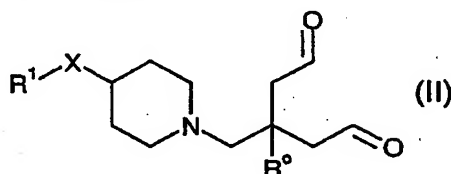
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12. A compound of formula (I) as claimed in any preceding claim wherein heterocyclyl is indolyl, imidazolyl, thienyl or pyridinyl.

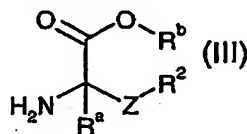
13. A process for preparing a compound of formula (I) as claimed in claim 1 comprising:

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a. reacting a compound of formula (II):



with a compound of formula (III):



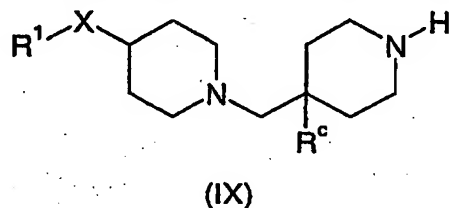
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in the presence of  $\text{NaBH}(\text{OAc})_3$  or  $\text{NaBH}_3(\text{CN})$  in a suitable solvent at a suitable temperature;

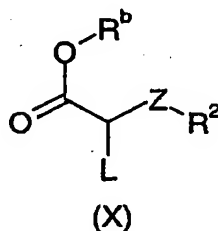
b. when  $\text{R}^b$  is not hydrogen, reacting a compound of formula (II) with a compound of formula (III), where  $\text{R}^b$  is not hydrogen, in the presence of

$\text{NaBH}(\text{OAc})_3$  in the presence of a suitable base in a suitable solvent at a suitable temperature;

- c. when  $\text{R}^a$  represents H, reacting a compound of formula (IX):

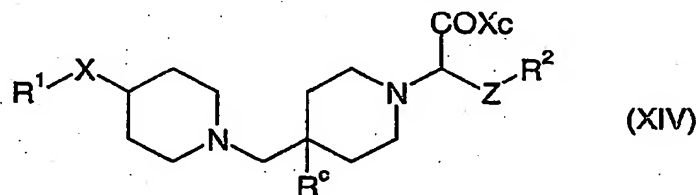


- 5 with a compound of formula (X):



wherein L is a suitable leaving group, in a suitable solvent, at a temperature in the range  $0^\circ\text{C}$  to  $30^\circ\text{C}$ , in the presence of a base; or,

- d. when  $\text{R}^a$  represents H, hydrolysing a compound of formula (XIV):



wherein Xc is a chiral auxiliary, in a suitable solvent, at a temperature between  $10^\circ\text{C}$  and reflux of the solvent.

14. A pharmaceutical composition which comprises a compound of the formula (I), or  
 15 a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.
15. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, for use in therapy.

16. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.
- 5 17. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1.

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